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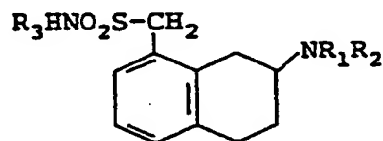
㉖ Applicant: **MERRELL DOW  
PHARMACEUTICALS INC.  
2110 East Galbraith Road  
Cincinnati Ohio 45215-6300 (US)**

㉗ Inventor: **Hibert, Marcel  
Domaine des Grands Prés, 21, rue Alfred  
Kastler  
F-67114 Eschau (FR)  
Inventor: Petty, Margaret A.  
5, rue Schimper  
F-67000 Strasbourg (FR)  
Inventor: Jones, C. Richard  
13, rue du Kochersberg, Willgottheim  
F-67370 Truchtersheim (FR)**

㉘ Representative: **Gillard, Marie-Louise et al  
Cabinet Beau de Loménie 55, Rue  
d'Amsterdam  
F-75008 Paris (FR)**

㉙ **8-Sulfamylmethylene-2-amino tetralins.**

㉚ The invention describes compounds of the formula



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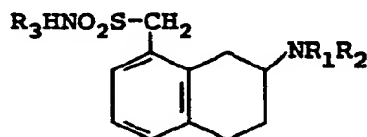
the enantiomers and mixtures thereof and the pharmaceutically acceptable salts thereof wherein R<sub>1</sub> and R<sub>2</sub> each represents hydrogen or lower alkyl, and R<sub>3</sub> is lower alkyl, as well as methods for their preparation and their use in the treatment of migraine.

**EP 0 451 008 A1**

## NOVEL 8-SULFAMYL METHYLENE-2-AMINO TETRALINS

This invention relates to novel 8-substituted-2-amino tetralins, to the methods for their preparation and to their use in the treatment of migraine.

More specifically, this invention relates to compounds of the formula



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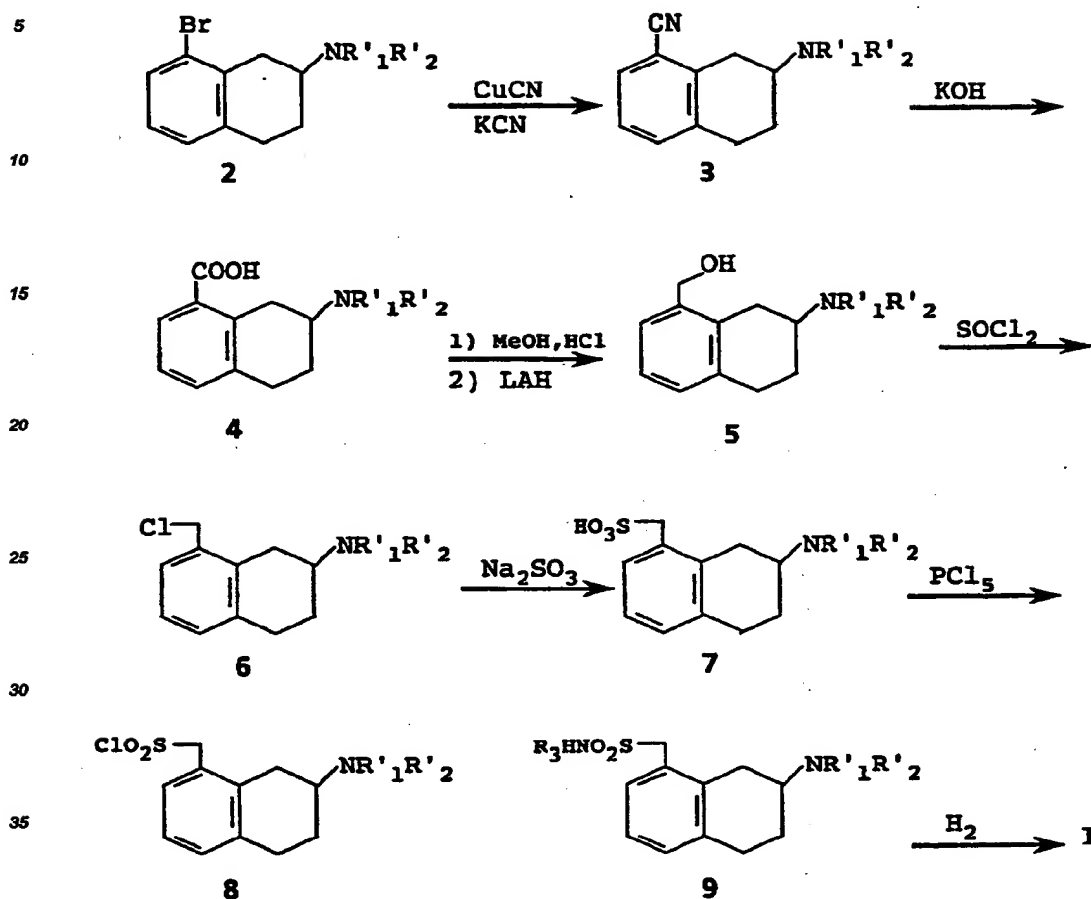
- 15 the enantiomers and mixtures thereof and the pharmaceutically acceptable salts thereof wherein  $R_1$  and  $R_2$  each represents hydrogen or  $C_{1-7}$  lower alkyl, and  $R_3$  is  $C_{1-7}$  lower alkyl.

The term lower alkyl includes the straight, branched-chain and cyclized alkyl moieties having up to 7 carbon atoms including cyclohexylmethyl, preferably propyl, methyl, ethyl and butyl. Pharmaceutically acceptable salts include all those salts normally utilized for pharmaceutical preparations, particularly those salts derived from organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, formates, mesylates, citrates, benzoates, fumarates, maleates, and salts with, e.g., p-toluene sulphonic acid.

The separation of the optical isomers can be achieved by such techniques as fractional distillation, chromatographic methods and preferably by enantio selective crystallization using optically pure acids such as (+) or (-) binaphthyl phosphonic acid. Typically the amine and optically pure binaphthyl phosphonic acid dissolved in acetone or warm isopropanol are mixed and maintained between 4 and 25°C until crystallization of one of the two diastereoisomeric salts. The solid is separated and recrystallized and the optically active free amine is recovered by extraction with ether from an aqueous solution of potassium carbonate. The other enantiomer is recovered from the mother liquors, basified and recrystallized with the other enantiomer of the binaphthyl phosphonic acid.

In their end-use application it is preferred to utilize the compounds in their enantiomeric pure state rather than mixtures thereof, although the mixtures are still useful but at increased dosages depending upon the proportionate mixture.

In general the compounds of this invention may be prepared by standard procedures analogously known in the art. In practice the preparations of these may conveniently be prepared by the following reaction scheme.

Reaction Scheme A

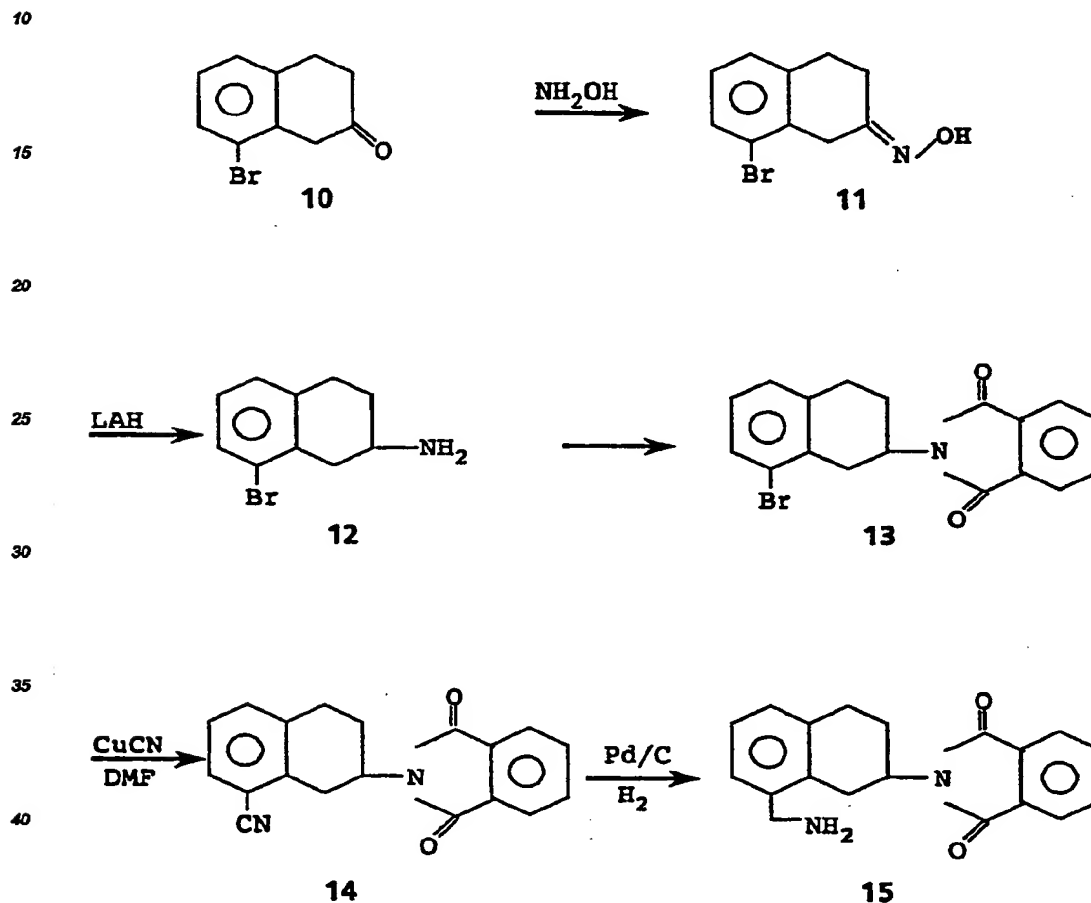
40 wherein  $R_1$ ,  $R_2$  and  $R_3$  are as previously defined and  $R'_1$  and  $R'_2$  are  $C_{1-7}$  alkyl or a removable amino protecting group, preferably benzyl, or together form a phthalamido protecting group (removed by treatment with hydrazine).

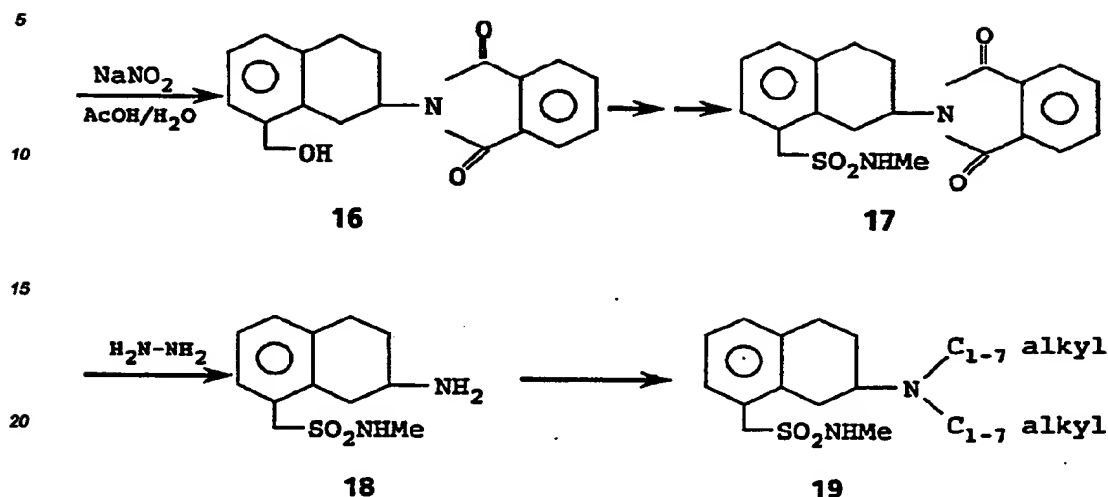
45 The synthesis is initiated by the reaction of 8-bromo-2- $R'_1R'_2$  aminotetralins with copper cyanide to obtain the corresponding 8-cyano aminotetralins, said reaction being effected by standard nucleophilic replacement reactions well known in the art. The resulting 8-cyano compounds (3) are hydrolyzed to their corresponding acids (4) by reaction with a strong base such as potassium hydroxide and the resulting acids are esterified and reduced to the corresponding alcohols (5) using lithium aluminum hydride (LAH). These alcohols, upon treatment with thionyl chloride are converted to their methylchloride (6) which upon treatment with sodium sulfate yields the corresponding sulfonic acid (7) which upon treatment with phosphorous pentachloride, gives the sulfonyl chloride (8). The sulfonyl chloride is treated with the appropriate amine to produce the sulphonamide (9). In the event there are any N-protecting groups (e.g., benzyl) on the 2-position amine then such groups are readily removed by standard hydrogenation techniques to yield the desired compounds of Formula I. In those instances wherein it is desired to prepare compounds wherein  $R_1$  and  $R_2$  are both a  $C_{1-7}$  alkyl, e.g., di-n-propyl amino, it is preferred to alkylate the free amine (following removal of the  $R'_1$ ,  $R'_2$ -protecting groups) using an alkyl halide, preferably an alkyl iodide in a basic medium. Of course, it is also obvious that in those instances wherein it is desired to prepare a 2-position dialkyl amino (i.e.,  $R_1$  and  $R_2$  are a  $C_{1-7}$  alkyl) then it may also be convenient to start with compounds of formula (2) wherein  $R'_1$  and  $R'_2$  represent a  $C_{1-7}$  alkyl. In those instances

wherein it is desired to prepare compounds wherein one of  $R_1$  and  $R_2$  is H, then it is preferred to utilize the process of the foregoing reaction scheme wherein  $R'_1$  is a protecting group and  $R_2$  is the desired  $C_{1-7}$  alkyl moiety. The foregoing reactions are standard reactions very familiar to those of ordinary skill in the art, the reaction conditions of which being specifically illustrated by the specific examples herein detailed.

Alternatively, the compounds may be synthesized by the procedures depicted in the following reaction scheme.

### Reaction Scheme B



Reaction Scheme B cont'd

In essence, Reaction Scheme B represents a series of reactions analogously known in the art wherein compound (10) is converted to its oxime, the oxime reduced with lithium aluminum hydride (LAH), the amine protected by its conversion to its phthalamido derivative (13), the bromo replaced with a cyano radical by reaction with cuprous cyanide in dimethyl formamide, the cyano moiety of (14) is converted to its amine by catalytic hydrogenation (Pd/C), the resulting aminomethyl radical is converted to its hydroxymethyl by reaction with sodium nitrite in acetic acid and water, and as in reaction Scheme A, the hydroxymethyl moiety is converted to its methylsulfonylmethyl derivative (17) which upon treatment with hydrazine, the phthalamido protecting group is removed to yield the desired product (18). In practice it is also advantageous to utilize a trifluoroacetamide as a protecting group which may be removed by standard procedures. The resulting product (18) may then be converted to its dialkylamino derivative (e.g. its di-n-propyl derivative) by reaction with an appropriate alkyl halide (e.g., 1-iodo propane) in a basic medium at slightly elevated temperatures.

The following examples detail the foregoing reaction schemes.

Example 140 2-Dimethylamino-8-cyano-1,2,3,4-tetrahydronaphthalene

Under nitrogen, 2-dimethylamino-8-amino-1,2,3,4-tetrahydronaphthalene (24 mmol) is dissolved in 33% sulfuric acid (120 mmol) and cooled down to  $0^\circ\text{C}$ . Sodium nitrite (24 mmol) in water (5 mmol) is carefully added under stirring at  $0^\circ\text{C}$ . After 30 minutes at this temperature, the mixture is slowly poured into a solution of cuprous cyanide (32 mmol) and sodium cyanide (177 mmol) in water (40 ml) warmed at  $50^\circ\text{C}$ .

The mixture is stirred at  $50^\circ\text{C}$  for one hour under a nitrogen atmosphere and then poured into 500 ml iced water. The pH of the solution is brought to 10 with 2N sodium hydroxide. Extraction with dichloromethane, washing of the organic phase with water, drying over sodium sulfate and evaporation to dryness affords the crude expected product. Purification by flash chromatography on silica gel (using toluene/methanol as eluent) affords the pure expected product.

Example 255 2-Dimethylamino-1,2,3,4-tetrahydronaphthalene-8-carboxylic acid

2-Dimethylamino-8-cyano-1,2,3,4-tetrahydronaphthalene (1 mmol), potassium hydroxide (2 mmol) and water (2 mmol) in ethylene glycol (1 ml) are warmed at  $150^\circ\text{C}$  for 20 hours under a nitrogen atmosphere. After

cooling, water is added and the aqueous phase is extracted with dichloromethane, acidified to pH 1-2 with 1N hydrochloride and extracted again with dichloromethane. Ammonia (25%) is then used to bring the pH of the aqueous phase to 5. Water is then evaporated under vacuum and the solid residue is taken up in dry tetrahydrofuran. The insoluble salts are filtered and tetrahydrofuran evaporated to dryness, yielding the expected acid as an oil.

### Example 3

#### 2-Dimethylamino-8-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene

2-Dimethylamino-1,2,3,4-tetrahydronaphthyl-8-carboxylic acid (1.1 mmol) is dissolved in 30 ml of dry methanol. A saturated solution of hydrochloride in ether (3 ml) is added and the mixture is stirred at room temperature for 24 hours. The solvents are evaporated under vacuum and the residue is dissolved in dichloromethane. Successive washing with 0.1N sodium hydroxide followed by drying over sodium sulfate and evaporation leads to the expected product as a colorless oil.

### Example 4

#### 2-Dimethylamino-8-hydroxymethyl-1,2,3,4-tetrahydronaphthalene

Lithium aluminum hydride (0.4 mmol) is suspended under argon atmosphere in dry ether. A solution of 2-dimethylamino-8-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene (0.7 mmol) in ether (1 ml) is added, the mixture is stirred at room temperature for 5 hours. A saturated solution of sodium sulfate in water is then added. After stirring for 30 minutes the mixture is extracted with ethyl acetate and dichloromethane. After drying over sodium sulfate, the organic phase is evaporated to dryness. Purification by flash chromatography on silica gel (methylene chloride/methanol) affords the pure expected product as an oil.

### Example 5

#### 2-Dimethylamino-8-chloromethyl-1,2,3,4-tetrahydronaphthalene

2-Dimethylamino-8-hydroxymethyl-1,2,3,4-tetrahydronaphthalene hydrochloride (1 mmol) is dissolved in thionyl chloride (5 ml) at 0°C and the mixture is stirred overnight at room temperature. The mixture is evaporated to dryness and the residue is dissolved with ether and water. The aqueous phase is washed with ether, basified with potassium bicarbonate and extracted with ethyl acetate. The organic extract is then washed with water, dried over sodium sulfate and evaporated to dryness, to yield the expected chloride which is used without further purification.

### Example 6

#### 2-Dimethylamino-8-sulfinomethyl-1,2,3,4-tetrahydronaphthalene

2-Dimethylamino-8-chloromethyl-1,2,3,4-tetrahydronaphthalene hydrochloride (3.0 mmol) and sodium sulfite (3.3 mmol) in water (15 ml) are warmed under reflux for 2 hours. After cooling and concentration the product precipitates, is filtered, washed with acetone and ether, dried under vacuum and used as such for the next step.

### Example 7

#### 2-Dimethylamino-8-chlorosulfonylmethyl-1,2,3,4-tetrahydronaphthalene

2-Dimethylamino-8-sulfinomethyl-1,2,3,4-tetrahydronaphthalene hydrochloride (2.75 mmol) and phosphorous pentaiodide (3.2 mmol) are mixed at 0°C. The addition is exothermic. The mixture is progressively warmed and maintained at 80°C for 1.5 hours. Most of phosphoryl chloride is eliminated by evaporation under vacuum (16 mmHg). The mixture is then cooled in an ice bath and water is carefully added to the oily residue. The mixture is then evaporated to dryness under vacuum and used as such for the next step.

Example 8-2-dimethylamino-8-methylaminosulfonylmethyl-1,2,3,4-tetrahydronaphthalene

5        2-Dimethylamino-8-chlorosulfinomethyl-1,2,3,4-tetrahydronaphthalene (approximately 2.7 mmol) in dry tetrahydrofuran is added to an excess of methylamine in dry tetrahydrofuran under stirring at -20°C. A solid precipitates, the mixture is stirred at room temperature for 12 hours. After evaporation to dryness, the crude solid is dissolved in water and methylene chloride. The organic phase is washed with 5% ammonium hydroxide and brine, dried over sodium sulfate and concentrated to dryness. The crude oil which is obtained is purified  
10 by flash chromatography on silica gel (eluent: gradient of methanol in methylene chloride). The hydrochloride of the pure free base is prepared in hydrochloride/isopropanol and recrystallized from methanol/ethyl acetate/ether.

Example 9

15        8-Bromo-2-tetralone, oxime

8-Bromo-2-tetralone (10 mmol) is dissolved in chloroform. Oxime hydrochloride (12 mmol) in water is added. The mixture is vigorously stirred for 12 hours. The organic phase is recovered, washed with 10% sodium  
20 bicarbonate and brine and evaporated to dryness to afford the expected product.

Example 102-Amino-8-bromo-1,2,3,4-tetrahydronaphthalene

25        Lithium aluminum hydride (3 mmol) is suspended in ether under an argon atmosphere. The oxime of 8-bromo-2-tetralone (10 mmol) in ether is added dropwise under stirring at 0°C. After 5 hours at room temperature, a minimum amount of a saturated solution of sodium sulfate in water is added. Dry sodium sulfate is added and the solid residue is extracted with ethyl acetate. The amine is extracted with 10% hydrochloride, basified  
30 with 10% sodium hydroxide and extracted with dichloromethane. Drying over sodium sulfate and evaporation leads to the pure expected amine.

Example 11

35        2-Phthalimido-8-bromo-1,2,3,4-tetrahydronaphthalene

2-Amino-8-bromo-1,2,3,4-tetrahydronaphthalene (10 mmol) is dissolved in dichloromethane (50 ml) with triethylamine (25 mmol) at 0°C. Dichlorophthalyl chloride (10 mmol) in dichloromethane (30 ml) is slowly added under rapid stirring. The mixture is stirred at 0°C for 30 minutes and at room temperature for 3 hours. Ether, in  
40 excess, is added, the precipitated solid is filtered. The organic phase is washed with 5% sodium hydroxide, 5% hydrochloride and brine, dried over sodium sulfate and evaporated to dryness to afford the expected compound.

Example 12

45        2-Phthalimido-8-cyano-1,2,3,4-tetrahydronaphthalene

2-Phthalimido-8-bromo-1,2,3,4-tetrahydronaphthalene (1 mmol) and cuprous cyanide (1.2 mmol) are refluxed in dimethylformamide for 6 hours. The resulting hot brown mixture is poured into a solution of hydrated  
50 ferric chloride and concentrated hydrochloride in water. The mixture is stirred at room temperature for 30 minutes, to decompose the complex. An excess of water is added and the mixture is extracted with toluene and ether. The organic phase is washed with water, 10% potassium carbonate and brine, dried over sodium sulfate and evaporated to dryness. The crude product is purified by flash chromatography (ethyl acetate/dichloromethane as eluent).

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Example 132-Phthalimido-8-aminomethyl-1,2,3,4-tetrahydronaphthalene

5        2-Phthalimido-8-cyano-1,2,3,4-tetrahydronaphthalene (8 mmol) is dissolved in ethanol. Methyl bisulfite (8 mmol) and 10% Pd over charcoal (50 mg) are added. Hydrogenation at atmospheric pressure yields the title amine as the methanesulfonate salt.

Example 14

10        2-Phthalimido-8-hydroxymethyl-1,2,3,4-tetrahydronaphthalene

15        2-Phthalimido-8-aminomethyl-1,2,3,4-tetrahydronaphthalene (8 mmol) is dissolved in diluted acetic acid. Sodium nitrite (8.5 mmol) in water is added. The reaction is stirred at room temperature for 3 hours and extracted with ether. The organic phase is washed with 5% hydrochloride, 5% sodium hydroxide and brine, dried over sodium sulfate and evaporated to dryness. The expected alcohol is purified by flash chromatography (ethyl acetate/dichloromethane as eluent) and is obtained pure as a colorless oil.

Example 15

20        2-Phthalimido-8-methylaminosulfonylmethyl-1,2,3,4-tetrahydronaphthalene

25        Following essentially the same procedure as for Examples 5 to 8 but substituting 2-phthalimido-8-hydroxymethyl-1,2,3,4-tetrahydronaphthalene for 2-dimethylamino-8-hydroxymethyl-1,2,3,4-tetrahydronaphthalene, the title compound is prepared.

Example 16

30        2-Amino-8-methylaminosulfonylmethyl-1,2,3,4-tetrahydronaphthalene

35        2-Phthalimido-8-methylaminosulfonylmethyl-1,2,3,4-tetrahydronaphthalene is dissolved in ethyl acetate. Hydrazine hydrate (1.05 equivalent) is added and the mixture is refluxed for 3 hours. The solvent is evaporated and the crude solid is dissolved in methanol (20 ml). Concentrated hydrochloride (1 ml) is added and the mixture is stirred at room temperature for 2 hours. After evaporation to dryness, the solid residue is dissolved in water and ethyl acetate. The aqueous phase is washed with ethyl acetate, basified with 5% sodium hydroxide and extracted with dichloromethane. The organic phase washed with water and brine, dried over sodium sulfate and evaporated to dryness will afford the expected amine as an oil. Purification by flash chromatography (methanol/ethyl acetate as eluent) and recrystallization of the hydrochloride salt from isopropanol/ethyl acetate/ether will afford the pure title compound.

Example 17

40        2-(N,N-Methyl-benzylamino)-8-methylaminosulfonylmethyl-1,2,3,4-tetrahydronaphthalene

45        Following essentially the procedure of Examples 1 to 8 but substituting 2-[N,N-methyl-benzylamino]-8-methylaminosulfonylmethyl-1,2,3,4-tetrahydronaphthalene (10 mmol) for 2-dimethylamino-8-bromo-1,2,3,4-tetrahydronaphthalene, the title compound is prepared.

Example 18

50        2-Methylamino-8-methylaminosulfonylmethyl-1,2,3,4-tetrahydronaphthalene

55        2-(N,N-methyl-benzylamino)-8-methylaminosulfonylmethyl-1,2,3,4-tetrahydronaphthalene (10 mmol) is dissolved in ethanol with methane sulfonic acid (10 mmol). The mixture is hydrogenated under atmospheric pressure to afford the title compound as a methane sulfonic salt.



Example 192-(N',N'-Dipropylamino)-8-methylaminosulfonylmethyl-1,2,3,4-tetrahydronaphthalene

5 The primary amine of Example 16 (120 mg, 0.47 mmol) is suspended in acetonitrile (7 ml) under an argon atmosphere. Triethylamine (0.43 ml, 3 mmol) and 1-iodo-propane (0.21 ml, 2.1 mmol) are added, and the mixture is warmed under reflux overnight. The resulting mixture is concentrated to dryness, extracted with methylene chloride, washed with 5% sodium carbonate, dried over sodium sulfate and evaporated to dryness. The resulting crude compound is purified by flash chromatography on silica gel using MeOH/CH<sub>2</sub>Cl<sub>2</sub> : 5/95 as  
 10 eluent. The pure amine is obtained as a yellow oil (120 mg, 75%) which crystallizes. The oxalate salt is crystallized from Et<sub>2</sub>O/i-PrOH.  
 m.p. 149°C.

In general the compounds of this invention represent a very select sub-group of compounds which are generically embraced within the scope of European Patent Application 0 272534-A2. However, EPO Application  
 15 0 272534 does not specifically teach any compound within the scope of this application nor does it specifically illustrate how the compounds of this application can be prepared.

In general the compounds of this invention are potent and selective 5HT<sub>1</sub>-like agonists useful in treating and/or preventing pain putatively associated with abnormal cranial vascular flow changes, particularly in migraine and related disorders such as for example, cluster headache.

20 Using standard *in vitro* and *in vivo* laborating essay methodology for testing compounds for their potential use in the treatment of migraine as well as by comparison with compounds known to have a beneficial effect in patients suffering from migraine and related disorders, it is determined that the compounds of this invention will be useful at doses in the range of about 0.25 to 100 mg per kilogram of body weight per day, preferably 0.5 to 20 mg per kilogram of body weight per day. The compounds may be administered in divided daily doses,  
 25 generally 3 to 4 times per day. Of course, it is to be appreciated that it may be necessary to make routine variations to the dosages depending on the age and weight of the patient, as well as the severity of the condition to be treated. Although calculations of doses are naturally predicated on the weight of the base, it is preferred that the compounds be administered in the form of a pharmaceutically acceptable salt, preferably those salts formed with hydrochloric, hydrobromic, succinic and methanesulfonic acid.

30 The compounds of the invention may be formulated for parenteral administration by injection, preferably intravenous or subcutaneous injection, e.g., by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing  
 35 agents and/or agents to adjust the tonicity of the solution. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as coco butter or other glycerides.

Tablets for sub-lingual administration may be formulated in a similar manner to those for oral administration.  
 40 For intra-nasal administration the compounds of the invention may be used as a liquid spray or in the form of drops.

Dosages of the compounds of the invention for rectal, sublingual or intranasal administration to man (of average body weight e.g., about 70 kg) for the treatment of migraine may be similar to those described previously for oral administration.

45 For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or  
 50 insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Aerosol formulations are preferably arranged as that each metered dose or "puff" delivered from a pressurized aerosol contains 0.2 mg to 2 mg of a compound of the invention, and each dose administered via capsules and cartridges in an insufflator or an inhaler contains 0.2 mg to 20 mg of a compound of the invention.  
 55 Administration may be several times daily, for example from 2 to 8 times, giving, for example, 1, 2 or 3 doses, each time. The overall daily dose by inhalation will be similar to that for oral administration.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents, such as analgesics, anti-inflammatory agents and antinauseants.

Additionally, the compounds of this invention may be utilized for the treatment of hypertension, depression and mania using doses based upon standard *in vitro* and *in vivo* assay methodology, said doses being within the same range as outlined above.

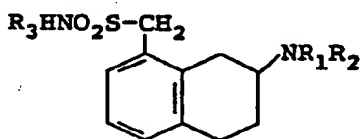
Accordingly, the invention also provides a pharmaceutical composition adapted for use in medicine which comprises the compound of formula (I) and/or a physiologically acceptable salt or solvate (e.g., hydrate) thereof, formulated for administration by any convenient route. Such compositions may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients. The compounds according to the invention may be formulated for oral, sublingual, parenteral, rectal or intra-nasal administration, or in a form suitable for administration are preferred.

The pharmaceutical compositions for oral administration may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose) fillers (e.g., lactose, sucrose, mannitol, corn starch, microcrystalline cellulose or calcium hydrogen phosphate) lubricants (e.g., stearic acid, polyethylene glycol, magnesium stearate, talc or silica), disintegrants (e.g., potato starch, sodium starch glycolate or croscarmellose sodium), or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, aqueous or oily solutions, syrups, elixirs, emulsions or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives, glucose/sugar syrup, gelatin, aluminium stearate gel, or hydrogenated edible fats), emulsifying agents (e.g., lecithin acacia or sorbitan mono-oleate), non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid). The liquid preparations may also contain conventional buffers flavoring, coloring and sweetening agents as appropriate.

As is true for any class of compounds suitable for use as pharmaceutically effective agents, certain members are preferred over others. In this instance it is preferred that  $R_3$  is methyl or ethyl while it is preferred that both  $R_1$  and  $R_2$  are both n-propyl or methyl, or  $R_1$  is hydrogen and  $R_2$  is methyl, n-propyl, ethyl or butyl.

### Claims

1. A compound of the formula



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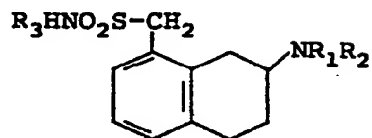
the enantiomers and mixtures thereof and the pharmaceutically acceptable salts thereof wherein  $R_1$  and  $R_2$  each represents hydrogen or  $C_{1-7}$  lower alkyl, and  $R_3$  is  $C_{1-7}$  lower alkyl.

2. A compound of claim 1 wherein  $R_1$  and  $R_2$  are  $C_{1-7}$  alkyl.
3. A compound of claim 1 wherein  $R_1$  and  $R_2$  are H.
4. A compound of claim 1 wherein  $R_1$  is H and  $R_2$  is  $C_{1-7}$  alkyl.
5. A compound of claim 1 wherein  $R_1$  and  $R_2$  are n-propyl.
6. A compound of claim 5 wherein  $R_3$  is methyl.
7. A compound of claim 1 wherein  $R_1$ ,  $R_2$  and  $R_3$  are methyl.

8. A compound of claim 1 wherein  $R_1$  is H and  $R_2$  is methyl.

9. A method for preparing a compound of the formula

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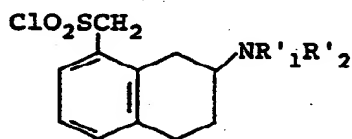
the enantiomers and mixtures thereof and the pharmaceutically acceptable salts thereof wherein  $R_1$  and  $R_2$  each represents hydrogen or  $C_{1-7}$  lower alkyl, and  $R_3$  is  $C_{1-7}$  lower alkyl,

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which comprises

(a) reacting a compound of the formula

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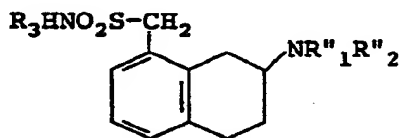
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with an amine of the formula  $NH_2R_3$ ,

wherein  $R'_1$  and  $R'_2$  are H,  $C_{1-7}$  alkyl or an amino protecting group, followed by the removal of any protecting group,

(b) N-alkylating a compound of the formula

30



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with a  $C_{1-7}$  alkyl halide

wherein  $R''_1$  is H,  $C_{1-7}$  alkyl or an amino protecting group, and  $R''_2$  is H, followed by the removal of any amino protecting group.

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10. The use of the compounds of claims 1 to 8 as pharmaceutically active agent.

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EP 0 451 008 A1



European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number

EP 91 40 0770

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	WO-A-8 404 247 (RORER INTERNATIONAL)		C 07 C 311/35
A	DE-A-3 320 521 (GLAXO)		A 61 K 31/18
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 C 311/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 14-06-1991	Examiner ZAROKOSTAS K.
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone  Y : particularly relevant if combined with another document of the same category  A : technological background  O : non-written disclosure  P : intermediate document</p> <p>T : theory or principle underlying the invention  E : earlier patent document, but published on, or after the filing date  D : document cited in the application  L : document cited for other reasons  &amp; : member of the same patent family, corresponding document</p>			

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